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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,052	04/09/2007	Paul A. Bunn Jr.	2848-65-PUS	7009

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,052	BUNN JR. ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,49,51-53,55-59 and 66-75* is/are pending in the application.

4a) Of the above claim(s) *51,52,59,68-72 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,49,53,55-58,66,67,73 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/24/06; 1/30/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restriction

The Election filed 1/29/08 in response to the Office Action of 11/29/07 is acknowledged and has been entered. Applicant elected group I without traverse. Applicant further elected the species E-cadherin (SEQ ID NO:3) with traverse.

The traversal is on the ground(s) that a search and examination of all of the species would not impose a serious burden on the examiner. This is not found persuasive. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record. There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 66-75 have been newly added by Applicant.

Claims 48, 49, 51-53, 55-59, 66-75 are pending.

Claims 51, 52, 59, 68-72, and 75 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 48, 49, 53, 55-58, 66, 67, 73, and 74 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48, 49, 53, 55, 56, 66, 67, 73, and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 66 and dependent claims 48, 49, 53, 55, 56, 67, 73, and 74 are rejected because claim 66 recites a method comprising determining whether expression levels of genes in a sample are "more similar to the expression level of the gene or genes that has been correlated with sensitivity to the EGFR inhibitor than to resistance to the EGFR inhibitor". The claims do not particularly point-out or distinctly claim which expression levels of genes have been correlated with sensitivity to the EGFR inhibitor and which expression levels of genes have been correlated with resistance to the EGFR inhibitor.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48, 49, 53, 55-58, 66, 67, 73, and 74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to select a

non-small cell lung cancer patient who is predicted to benefit from therapeutic administration of gefitinib comprising detecting the level of E-cadherin polynucleotides in a sample of tumor cells from said patient, comparing said level to a level of E-cadherin polynucleotides in a sample of tumor cells from a subject that is resistant to gefitinib, and selecting the patient as being predicted to benefit from therapeutic administration of gefitinib if the level of E-cadherin polynucleotides in the sample of tumor cells from said patient is higher than the level of E-cadherin polynucleotides in the sample of tumor cells from a subject that is resistant to gefitinib, **the specification does not reasonably provide enablement for** methods to select a patient with just any cancer who is predicted to benefit from therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor, comprising detecting polynucleotide or polypeptide expression levels of E-cadherin in a sample of tumor cells from a patient, comparing the levels to just any level of expression of E-cadherin that anyone has correlated with sensitivity or resistance to just any EGFR inhibitor, and selecting the patient as being predicted to benefit from a therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor if the polynucleotide or polypeptide expression level of E-cadherin in the patient's tumor cells is statistically more similar to just any expression level of E-cadherin that anyone has correlated with sensitivity to just any EGFR inhibitor than to resistance of just any EGFR inhibitor. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods to select a patient with just any cancer who is predicted to benefit from therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor, comprising detecting polynucleotide or polypeptide expression levels of E-cadherin in a sample of tumor cells from a patient, comparing the levels to just any level of expression of E-cadherin that anyone has correlated with sensitivity or resistance to just any EGFR inhibitor, and selecting the patient as being predicted to benefit from a therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor if the polynucleotide or polypeptide expression level of E-cadherin in the patient's tumor cells is statistically more similar to just any expression level of E-cadherin that anyone has correlated with sensitivity to just any EGFR inhibitor than to resistance of just any EGFR inhibitor. It is noted that drugs having

substantially similar biological activity as an EGFR inhibitor broadly encompass every drug that treats cancer, as treating cancer is a biological activity of EGFR inhibitors.

The specification teaches a method to select a non-small cell lung cancer patient who is predicted to benefit from therapeutic administration of gefitinib comprising detecting the level of E-cadherin polynucleotides in a sample of tumor cells from said patient, comparing said level to a level of E-cadherin polynucleotides in a sample of tumor cells from a subject that is resistant to gefitinib, and selecting the patient as being predicted to benefit from therapeutic administration of gefitinib if the level of E-cadherin polynucleotides in the sample of tumor cells from said patient is higher than the level of E-cadherin polynucleotides in a sample of tumor cells from a subject that is resistant to gefitinib (see page 42, in particular). In regards to claims such as 57, 58, and 74, drawn to methods wherein *any* expression of E-cadherin is predictive of a benefit from EGFR inhibitor, it is noted that the specification discloses that *both* gefitinib-sensitive and gefitinib-resistant patients express E-cadherin polynucleotides (see page 42, in particular). Therefore, the specification provides evidence that the claimed methods are not enabled in commensurate with the scope of the claims. Further, the specification does not demonstrate the claimed method using E-cadherin expression levels in just any cancer, using levels of E-cadherin polypeptide expression levels, or comparisons using just any level of expression of E-cadherin that could possibly be correlated with sensitivity or resistance to just any EGFR inhibitor.

It is noted that the instant disclosure does not demonstrate that E-cadherin polypeptide levels correlate with E-cadherin polynucleotide levels. One of skill in the art

would not predict that the E-cadherin polynucleotide levels are indicative of E-cadherin polypeptide levels, as evidence abounds in which protein levels do not correlate with alterations in mRNA levels. There are many steps in the pathway leading from DNA to protein, and all of them can, in principle, be regulated. For example, Alberts *et al.* (Molecular Biology of the Cell, 3rd edition, 1994, page 465) illustrate post-transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Lewin, B. also teaches (Genes VI, Oxford University Press, Inc., NY, Chapter 29, 1997) that a major control point for genes exists during the initiation of transcription by the interaction of the RNA polymerase with its promoter. Concurring with Alberts *et al.*, Lewin further acknowledges downstream control of gene expression since translation of mRNA in the cytoplasm is also a point of control. Also, with regards to tumor associated antigens, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Furthermore, Mallampalli *et al.* (Biochem. J. Vol. 318, 1996, pages 333-341) teach that the glucocorticoid, betamethasone, increased mRNA expression of cholinephosphate cytidylyltransferase (CT) as determined by RT-PCR and Southern analysis, but did not *alter* the levels of the polypeptide, i.e. the CT enzyme as assayed by Western blotting (abstract, and page 339, 2nd column, 2nd paragraph). Further, Lewin acknowledges that control of gene

expression can occur at multiple stages and that production of RNA *cannot inevitably* be equated with production of protein. Finally, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Thus, the predictability of protein translation

and its possible use as an indicator of efficacy of treatment cannot predictably be determined by levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

The state of the prior art dictates that if a molecule such as E-cadherin polynucleotide is to be used as a surrogate for a particular diseased state (such as a non-small cell lung cancer patient who is predicted to benefit from therapeutic administration of gefitinib), there must be a particular expression pattern that would allow E-cadherin polynucleotide to be used as an indication of said particular diseased state. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. While Tockman et al is drawn to using a particular biomarker to diagnose a particular disease, the teachings of Tockman et al exemplify the state of the prior art for using a particular molecule to indicate a particular diseased state. In the instant situation, the particular diseased state is a cancer that is resistant or responsive to a particular type of therapy. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known

(histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of a correlation between expression of a particular molecule and a particular diseased state, one of skill in the art would not be able to predictably be able to use said particular molecule to identify said particular diseased state without undue experimentation.

The level of unpredictability for using a particular molecule to identify a patient that would be responsive to a particular therapy is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and every type of cancer, methods using E-cadherin polypeptide expression, every type of EGFR inhibitor and agonist thereof, every type of drug having substantially similar biological activity as just any EGFR inhibitor, and methods comprising using just any level of expression of E-cadherin that anyone has correlated with sensitivity or resistance to just any EGFR inhibitor, a practitioner wishing to practice

the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods to select a patient with just any cancer who is predicted to benefit from therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor, comprising detecting polynucleotide or polypeptide expression levels of E-cadherin in a sample of tumor cells from a patient, comparing the levels to just any level of expression of E-cadherin that anyone has correlated with sensitivity or resistance to just any EGFR inhibitor, and selecting the patient as being predicted to benefit from a therapeutic administration of just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor if the polynucleotide or polypeptide expression level of E-cadherin in the patient's tumor cells is statistically more similar to just any expression level of E-cadherin that anyone has correlated with sensitivity to just any EGFR inhibitor than to resistance of just any EGFR inhibitor, and Applicant has not enabled said methods because it has not been shown that levels of E-cadherin polypeptides and polynucleotides in tumor cells from a patient with just any cancer statistically more similar to just any expression level of E-cadherin that anyone has correlated with sensitivity to just any EGFR inhibitor than to resistance of just any EGFR inhibitor would predictably determine that said patient would benefit from therapeutic administration of

just any EGFR inhibitor, just any agonist thereof, or just any drug having substantially similar biological activity as just any EGFR inhibitor.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 48, 49, 53, 55-58, 66, 67, 73, and 74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 11/781946. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-15

of copending Application No. 11/781946 are drawn to a species of instant claims 48, 49, 53, 55-58, 66, 67, 73, and 74.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

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